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URGENT !!!

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PCT/EP03/03540 WO 03/084520 EURO-CELTIQUE S.A.	E 7823 / WM	28 July 2004

In response to the Written Opinion dated 3 June 2004 the following submission is made on behalf of the applicant:

A set of new claims 1 to 32 is submitted herewith which replaces the original claims 1 to 32. However, applicant preserves the right to revert to the original claims at a later point in time.

New independent claim 1 has been amended by inserting the feature "in a substantially non-swellable diffusion matrix", which was mentioned in originally filed claim 8, and "comprising ethyl cellulose", mentioned, e.g. on p 18, l. 9 to 11.

New claim 8 was amended by deleting the feature "in a substantially non-swellable diffusion matrix".

The references of claims 9 and 10 were amended accordingly.

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1. Novelty

Applicant respectfully submits that the new claims on file are new in view of documents D1 to D5. According to the Guidelines for Examination in the European Patent Office, a document of the art can be novelty destroying only if the claimed subject matter is directly and unambiguously derivable from that document including any features implicit to a person skilled in the art (Part C, IV, 7.2). In the applicant's opinion, none of the documents D1 to D5 disclose a pharmaceutical formulation comprising oxycodone and naloxone in a non-swellable diffusion matrix comprising ethyl cellulose, wherein
the pharmaceutical formulation is storage stable
the matrix is a substantially non-swellable diffusion matrix comprising ethyl cellulose, and
the active compounds are released from said matrix in a sustained, invariant and independent manner.

D1 to D5 do not even disclose whether the matrices mentioned therein are diffusion matrices, let alone non-swellable diffusion matrices having the inventive features. There are many different types of matrices which differ depending on whether the active compound is released by pure diffusion or by erosion of a matrix. The presence of ethylcellulose and a fatty alcohol does not imply that the corresponding matrix is a diffusion matrix. Even diffusion matrices made from identical or similar matrix forming substances do not necessarily have the same release properties. In view of the foregoing fact, applicant is of the opinion that none of the documents referred to by the Examiner neither directly nor inherently does disclose the claimed subject matter or the inventive formulation having the afore-mentioned features.

D1: WO 99/32119

The Examiner holds the opinion that claims 1 – 32 are anticipated by D1 disclosing oral dosage forms comprising a combination of an orally analgesically effective amount of an

opioid agonist and an orally active opioid antagonist, the opioid antagonist being included in a ratio to the opioid agonist to provide a combination product, which is analgesically effective, when the combination is administered orally, but which is aversive in a physically dependent subject.

D1 mentions the use of oxycodone as the agonist and naloxone as an antagonist, which may be formulated in a sustained release matrix. However, it is not mentioned that the active compounds are released from the preparation in an invariant and independent manner. It is also not mentioned that the preparations of D1 are storage stable, as defined in the present patent application.

With respect to the sustained release matrix, it is described in D1 that the sustained release dosage form may optionally include a sustained release carrier, which is incorporated into a matrix along with the opioid agonist and opioid antagonist or may be applied as a sustained release coating. Furthermore, matrix bead formulations are mentioned, wherein a controlled release matrix is used. The matrix may comprise alkyl celluloses and fatty alcohols, but also polymers like cellulose ethers (Eudragit® RSPO), hydroxyalkyl celluloses, etc. are mentioned, which are explicitly excluded in the present patent application.

Regarding the process for preparing matrix-based beads, D1 discloses the preparation of granules by wet granulating hydroxyalkyl cellulose/opioid with water. It also mentions that spheroids may be prepared containing a water-insoluble polymer, especially an acrylic polymer, an acrylic copolymer or ethylcellulose.

Alternatively, the sustained release matrix may also be prepared by melt extrusion. It is mentioned that in order to obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g., ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material.

Thus, D1 not only does not unambiguously disclose a substantially non-swellable diffusion matrix releasing the active compounds in an invariant and independent manner, but even teaches that the preferred components according to the present invention as well as the explicitly excluded components of the present invention are equally suitable ingredients, such that the specific selection of components leading to a sustained release matrix providing an invariant and independent release of the active compounds is not disclosed by D1.

Thus, D1 does not anticipate claim 1 or 14, and therefore is also not novelty-destroying with respect to any of the sub-claims.

D2: WO 99/32120

D2 relates to a method of reducing the abuse potential of an oral dosage form of an opioid analgesic, wherein an analgesically effective amount of an orally active opioid agonist is combined with an opioid antagonist in an oral dosage form which would require at least a two-step extraction process to be separated from the opioid agonist, the amount of opioid antagonist included being sufficient to counteract opioid effects if extracted together with the opioid agonist and administered parenterally.

The disclosure of D2 is nearly identical to the disclosure of D1, such that the same applies as explained for D1. D2, therefore, also cannot be considered as novelty-destroying.

D3: WO 03/07802

D3 discloses a pharmaceutical composition comprising about 10 mg oxycodone hydrochloride and 0.80 to 0.90 mg naloxone hydrochloride in a dosage form that provides sustained release of at least the oxycodone hydrochloride.

However, D3 does not disclose pharmaceutical preparations in a substantially non-swellable diffusion matrix comprising ethyl cellulose providing an independent and invariant release according to new claim 1, neither in the description nor in the Examples.

With respect to the carriers used in D3 several substances are named, inter alia, ethylcellulose as well as fatty alcohols as components for the sustained release matrix, but also Eudragit or hydroxypropyl methylcellulose, which are explicitly excluded in the present patent application.

In Examples 1 to 8 of D3, there is even not one single composition described comprising ethyl cellulose, but only several types of Eudragit.

Thus, D3 not only does not unambiguously disclose a substantially non-swellable diffusion matrix releasing the active compounds in an invariant and independent manner, but also does not mention that this is achieved by a diffusion matrix comprising ethyl cellulose, which is only mentioned in a list of possible carriers, also comprising substances being explicitly excluded for the present invention, but obviously preferred by D3 as can be taken from the Examples.

Therefore, D3 does not anticipate the preparations of the present invention combining the features of a non-swellable diffusion matrix comprising ethyl cellulose and releasing the active agent in a sustained, independent and invariant manner.

D4: US 4,457,933

D4 relates to a method for decreasing the oral and parenteral abuse potential of strong analgetič agents such as, inter alia, oxycodone, by combining an analgesic dose of the agent

with naloxone in specific relatively narrow ranges, the oxycodone-naloxone compositions having a ratio of 2.5 to 5:1 parts per weight.

However, D4 remains completely silent with respect to the formulation of the active agents. Only in col. 4, l.5 to 21 of D4, it is mentioned that pharmaceutical compositions containing oxycodone and naloxone can be formulated according to conventional pharmaceutical practice to provide unit dosage forms which may include solid preparations suitable for oral administration as well as liquid preparations suitable for parenteral administration. With respect to the carrier substances, an inorganic carrier, e.g., talc or an organic carrier, such as lactose or starch, are named. Thus, D4 gives no indication on the use of sustained release formulations with release characteristics like independent and invariant release as claimed by the present invention, and does not even mention the compounds being used in these formulations according to the present invention, let alone a non-swellable diffusion matrix providing such characteristics.

Therefore, D4 is not relevant with respect to novelty of new claim 1 and any claims depending thereon being directed to the preparation in a non-swellable diffusion matrix, which was already confirmed by the Examiner not objecting to former claims 8 to 10 and 14 to 27 with respect to novelty.

D5: GB 1,390,772

D5 relates to pharmaceutical compositions suitable for oral administration comprising a compound having substantial narcotic activity, both orally and by injection, the compound being, inter alia, oxycodone, and a narcotic antagonist which is substantially less active orally than by injection, the narcotic antagonist being, inter alia, naloxone, the weight ratio of oxycodone to naloxone being 5:0.1, so that naloxone does not block the narcotic effect of

oxycodone when the composition is administered orally but prevents an acute euphoriant effect by the agonist when the composition is injected.

Thus, D5 might disclose pharmaceutical preparations comprising oxycodone and naloxone in amounts and ratios partially corresponding to those of the present invention but as in the case of D4, D5 does not describe any sustained release formulation in a non-swellable diffusion matrix. D5 only mentions that any conventional excipients in conventional amounts may be used. There is not the least indication on the use of sustained release formulations in a non-swellable diffusion matrix, let alone any formulations with independent and invariant release characteristics.

Thus, D5 does not anticipate new claim 1 or any claims depending thereon relating to formulations in a substantially non-swellable diffusion matrix like former claims 8 to 10, and 14 to 27, which were already considered as being new with respect to D5.

2. Inventive Step

Regarding lack of inventive step, we respectfully would like to point to the fact that D3 is published on 30 January 2003, i.e. later than the priority date of the present patent application, which is 5 April 2002, and, therefore, is not relevant with respect to inventive step.

D1 and D2 might describe sustained release formulations, but relate to a completely different problem, namely, the provision of an aversive effect in a physically dependent human subject abusing a medicament containing an opioid agonist by the addition of an opioid antagonist, and, thus, are completely silent regarding storage-stability of pharmaceutical preparations and specific release characteristics, such as the sustained, invariant and independent release of two specific active agents, namely, oxycodone and naloxone, let alone that this is achieved by the inventive preparations in a non-swellable diffusion matrix.

There is no indication on the release behaviour of the two active agents, if the amount of one of these agents is changed or the influence of different amounts on the release rates of both of these agents, or that these release characteristics may be controlled by a non-swellable diffusion matrix, as described in the present invention.

Thus, D1 as well as D2 do not suggest the present invention.

The same applies to D4 and D5, which do not even mention sustained release formulations, and, consequently, give no indication on how the characteristics of such formulations might be controlled.

Consequently, the Examiner is respectfully requested to approve patentability of the present invention in the International Preliminary Examination Report.

Encls.:

New claims 1 to 32

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EURO-CELTIQUE S.A.

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New Claims

1. A storage stable pharmaceutical preparation comprising oxycodone and naloxone in a substantially non-swellable diffusion matrix comprising ethyl cellulose, **characterized in that** the active compounds are released from the preparation in a sustained, invariant and independent manner.

2. Preparation according to claim 1,
characterized in that oxycodone and/or naloxone are present in the form of pharmaceutically acceptable and equally active derivatives such as the free base, salts and the like.

3. Preparation according to claim 2,
characterized in that that oxycodone and/or naloxone are present as their hydrochloride, sulfate, bisulfate, tatrate, nitrate, citrate, bitatrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate or succinate.

4. Preparation according to one of the preceding claims,
characterized in that oxycodone is present in excess referred to the unit dosage amount of naloxone.

5. Preparation according to one of the preceding claims,
characterized in that Naloxone is present in an amount range of 1 to 50 mg.

6. Preparation according to one of the preceding claims,
characterized in that oxycodone is present in an amount range of 10 to 150 mg, preferably of 10 to 80 mg.

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7. Preparation according to one of the preceding claims,
characterized in that oxycodone and naloxone are present in weight ratio ranges of maximal 25 : 1, preferably of maximal 20:1, 15:1, especially preferably of 5:1, 4:1, 3:1, 2:1 or 1:1.

8. Preparation according to one of the preceding claims,
characterized in that the preparation comprises a substantially non-erosive diffusion matrix.

9. Preparation according to claim 1 or 8,
characterized in that the diffusion matrix comprises at least ethylcellulose and at least one fatty alcohol as the components that essentially influence the release behaviour of the active compounds.

10. Preparation according to claim 1, 8 or 9,
characterized in that the preparation does not comprise relevant parts of alkaline and/or water-swellable substances, especially of derivatives of acrylic acid and/or hydroxyalkyl celluloses.

11. Preparation according to one of the preceding claims,
characterized in that the preparation contains usual fillers and additional substances, especially lubricants, flowing agents, plasticizers and the like.

12. Preparation according to claim 11,
characterized in that it comprises magnesium stearate, calcium stearate and/or calcium laureate and/or fatty acids, preferably stearic acid as the lubricant.

13. Preparation according to claim 11,
characterized in that it comprises highly-disperse silica, preferably Aerosil®, Talcum, corn starch, magnesium oxide and magnesium and/or calcium stearate as the flowing agent.

14. A storage stable pharmaceutical preparation comprising oxycodone and naloxone in a substantially non-swellable diffusion matrix,
characterized in that the matrix is influenced with respect to its substantial release characteristics by ethylcellulose and at least one fatty alcohol and that the preparation comprises oxycodone and naloxone in a weight ratio of maximal 25:1, preferably maximal 20:1, 15:1, especially preferably of 5:1, 4:1, 3:1, 2:1 or 1:1.

15. Preparation according to claim 14,
characterized in that oxycodone and naloxone are present in the form of pharmaceutically acceptable and equally active derivatives, such as the free-base, salts, and the like.

16. Preparation according to claim 15,
characterized in that oxycodone and naloxone are present as hydrochloride, sulfate, bisulfate, tatrate, nitrate, citrate, bitatrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate or succinate.

17. Preparation according to one of claims 14 to 16,
characterized in that oxycodone is present in excess referred to the unit dosage amount of naloxone.

18. Preparation according to one of claims 14 to 17,
characterized in that naloxone is present in an amount range of 1 to 50 mg.

19. Preparation according to one of claims 14 to 18,
characterized in that oxycodone is present in an amount range of 10 to 150 mg, preferably of 10 to 80 mg.

20. Preparation according to one of claims 14 to 19,
characterized in that the preparation comprises a substantially non-swellable and non-erosive diffusion matrix.

21. Preparation according to claim 20,
characterized in that the diffusion matrix comprises at least ethylcellulose and at least one fatty alcohol as the components that essentially influence the release behaviour of the active compounds.

22. Preparation according to claim 20 or 21,
characterized in that the preparation does not comprise relevant parts of alkaline and/or water-swellable substances, especially of derivatives of acrylic acid and/or hydroxy alkyl celluloses.

23. Preparation according to one of claims 14 to 22,
characterized in that the fatty alcohols comprise lauryl, myrestyl, stearyl, cetostearyl, ceryl and/or cetyl alcohol, especially preferably stearyl alcohol.

24. Preparation according to one of claims 14 to 23,
characterized in that the preparation comprises usual fillers and additional substances, especially lubricants, flowing agents, plasticizers and the like.

25. Preparation according to claim 24,
characterized in that it comprises magnesium stearate, calcium stearate and/or calcium laureat and/or fatty acids, preferably stearic acid as lubricant.

26. Preparation according to claim 24,
characterized in that it comprises highly dispersed silica, preferably Aerosil®, talcum, corn starch, magnesium oxide, magnesium stearate and/or calcium stearate as flowing agent.

27. Preparation according to one of the preceding claims,
characterized in that commercially available polymer mixtures which comprise ethylcellulose, preferably Surelease® E-7-7050 are used instead of ethylcellulose.

28. Preparation according to one of the preceding claims,
characterized in that the preparation has been formulated for oral, nasal, rectal application or for application by inhalation.

29. Preparation according to one of the preceding claims,
characterized in that the preparation is a tablet, pill, capsule, granule and/or powder.

30. Preparation according to one of the preceding claims,
characterized in that the preparation or precursors thereof are produced by build-up and/or break-down granulation.

31. Preparation according to one of claims 1 to 29,
characterized in that the preparation or precursors thereof are produced by extrusion.

32. Preparation according to one of the preceding claims,
characterized in that the preparation can be stored over a period of at least 2 years under standard conditions (60% relative humidity, 25°C) in accordance with admission guidelines.